Clinical Management Protocol for Nipah Virus Disease

Central Team
Ministry of Health and Family Welfare
Government of India

Dr Chandis

31/5/18.

Prepared by:

1. Dr AshutoshBiswas, Professor, Department of Medicine, AIIMS, New Delhi.
2. Dr Dipak Bhattacharya, Consultant, Department of Pulmonary Medicine, Safdarjung Hospital, New Delhi,
3. Dr. Naveen Gupta, Joint Director, HOD, Zoonoses division, National Centre for Disease Control, Delhi.
4. Dr Rima Sahay, Scientist B, Institute of Virology, Pune.
5. Dr.P.Ravindran, Addl DDG & Director, Emergency Medical Relief, DGHS, Ministry of Health, Government of India- Team Leader.

Clinical Management Protocol forNipahVirus Disease

1. Introduction:

Nipah virus (NiV) infection is an emerging zoonotic disease which was first recognized in a large outbreak of 276 reported cases in Malaysia and Singapore from September 1998 to May 1999.

In India, two outbreaks in human were reported from Siliguri (2001) and Nadia (2007), West Bengal.Fruit bats of *Pteropus* genus are the natural reservoir of NiV. There is circumstantial evidence of human-to-human transmission in India in 2001. During the outbreak in Siliguri, Forty-five (75%) of the 60 patients had a history of hospital exposure, i.e., they were members of the hospital staff or had attended to or visited patients in the hospital, suggesting nosocomial infection.

2. Epidemiology

2.1. Agent: NiV is a highly pathogenic paramyxovirus.

2.2. Natural Reservoir: Fruit bats of *Pteropus* genus are the natural reservoir of NiV. Pig is an amplifying host. It may become infected after consumption of partially bat eaten fruits that dropped in pigsty (as was evident in the Malaysia outbreak in 1998).

2.3. Host factors:
In Siliguri outbreak, all the 66 cases investigated by National Institute of Virology, Pune were above 15 years. In the current outbreak in Kerala, it is the economically productive age group which is involved and there is no sex differential.

2.4. Environmental Factors
Seasonality was strongly implicated in NiV outbreaks in Bangladesh and India. All of the outbreaks occurred during the months from December to May.

2.5. Mode of Transmission: Transmission of Nipah virus to humans may occur after direct contact with infected bats, infected pigs, or from other Nipah virus

infected people. Routes of transmission of Nipah virus have also been identified from its natural reservoir to human through drinking of raw date palm sap contaminated with NiV. However, human to human transmission has been attributed as one of the major modes of transmission in the epidemic in Siliguri and in the current outbreak in Kozhikode (Kerala)(May, 2018), India.

2.6. Incubation period: It varies from 4-21 days.

2.7. Period of Communicability: There is no clinical studies to suggest the period for which a patient will shed virus in different body fluids. In the absence of evidence, it is presumed that a person may be infective from the day of onset of symptoms till 21 days.

3. Pathogenesis.

The exact pathogenetic mechanism of Nipah infection is still not very clearly documented. Nipah infection primarily involves the blood vessels in the form of vasculopathy and vasculitis resulting in perivascular cellular infiltration, inflammation and necrosis. Due to high viremia it is very likely that several cytokines and chemokines are released causing vascular damage. Severity of the clinical symptoms and organ involvement are most likely dependent on the extent of vascular damage.

Post-mortem evaluation in one of the cases has revealed gross cerebral and pulmonary oedema. Cross-section of the brain and lungs showed evidence of gross pulmonary haemorrhage and cerebral congestion.

Pathological findings include :

- Vasculopathy and necrotizing vasculitis
- Cerebral oedema, with vascular congestion and focal haemorrhages.
- Pulmonary oedema with or without associated diffuse alveolar damage and haemorrhage.
- Neurons adjacent to vasculitic vessels may showeosinophilic infiltration and nuclear viral inclusions.
- In relapse cases, histopathology revealed cerebral oedema,

inflammation, endothelial syncytia, thrombosis and parenchymal necrosis.

4. Clinical features

4.1. Symptoms

Incubation period ofNipah infection is from 4 to 21 days. Initially non specific symptoms may be fever, headache, dizziness and vomiting. The hallmark of Nipah viral infection is the acute onset of following symptoms.

1. Moderate to high grade fever
2. Headache
3. Vomiting
4. Cough
5. Breathlessness
6. Change in behaviour/sensorium
7. Seizures/abnormal movement
8. Myalgia
9. Fatigue

In the Siliguri outbreak, the patients initially had fever (100%), headache and myalgia (57%), vomiting (19%), altered sensorium (confusion to coma, 97%), respiratory symptoms (tachypnea to acute respiratory distress, 51%), and involuntary movements or convulsions (43%).

In the current outbreak of Nipahvirus disease in Kerala it has been noted that most of the patients presented with moderate to high grade fever, headache often severe, vomiting and general weakness along with myalgia. Cough and breathlessness were also one of the presenting complaints seen in the majority of the patients. Breathlessness often progressed rapidly resulting in overt respiratory failure requiring use of supplementary oxygen and at times ventilator support. Respiratory failure requiring ventilator support was risk factors for high mortality.
Commonly observed neurological symptoms were headache, altered sensorium and seizures from the 3rd day of onset of fever. Most of the time headache was

associated with vomiting and altered behaviour.Thirty to forty percent of the patients presented with generalized or focal seizures which were controlled in most of the cases with the use of anticonvulsant medications.

Behavioural changes were often one of the initial presenting features before development of altered sensorium and unconsciousness. In a significant number of patients, the disease rapidly progresses to coma within five to seven days. Few cases may also show signs of cerebellar dysfunction.

Few patients also developed myocarditis, heart failure and pulmonary oedema often associated with or without cardiogenic shock. Coagulopathy may be seen in some of the cases with thrombocytopenia and raised d-Dimer.

4.2. Physical findings

Fever usually high grade and persists 5-7 days. In the Kozhikode, Kerala cohort, tachycardia and tachypnoea were noted in all of the patients and several of them progressed to overt respiratory distress with oxygen desaturation. At presentation most of the patients had normal blood pressure, no rashes, no haemorrhagic spot or bleeding from any sites.

Systemic examinationusually does not show any significant abnormalities. However, with the progress of the disease process there is often evidence of gradual fall in the haemodynamic parameters with failure of respiratory and cardiac compensatory mechanism evolving in to state of respiratory and cardiac failure. This is evident in the form of falling partial pressure of oxygen saturation levels and fall in blood pressure. Signs of overt cardiac failure may be present in some of the cases in early stages.

Conscious level could vary from fully alert to deeply unconsciousness. Feature of encephalitis or few cases of meningo-encephalitis may be present on 2nd or 3rd day onwards. Signs of meningeal irritation may not be present among these patients. Patients may be in altered sensorium, stuporous and violent behaviour.
On examination of the abdomen mild hepatomegaly with tenderness may be noted. On ultrasound or CT scan mild ascites and/or pleural effusion has been

found.

Kidneys in the early stages are spared. Renal failure are documented in the later stages due to complications. Multi-organ failure is usually found in the severe stages of the disease.

4.3. Post Nipah infection complications:

Psychiatric complications may be seen after full recovery. If the neurological signs and symptoms of encephalitis develop after more than 10 weeks of the initial exposure, it is known as late-onset encephalitis. Long term complication are seen in some case in the form of relapse of encephalitis months to years after recovery.

4.4. Laboratory Diagnosis

Laboratory diagnosis of a patient with a clinical history of NiV can be made during the acute and convalescent phases of the disease by using a combination of tests.

Laboratory confirmation of NiV infection either by:

i) IgM antibody against NiV identified in serum or CSF,
ii) NiV RNA identified by RT-PCR from respiratory secretions, urine or cerebrospinal fluid, or
iii) Isolation of NiV from respiratory secretions, urine or cerebrospinal fluid or other tissue specimens (only to be carried out in a BSL 4 Laboratory).

Tests at sr.No. (i) and (ii) can be carried out in a BSL 2 laboratory carrying BSL 3 precautions.

As it is a BSL -4 pathogen, the specimen collection and the triple layer packaging requires well trained staff. The procedure of sample collection and packaging is placed at **Annexure-I.**

4.5. Treatment

4.5.1. Guiding Principles

There is no confirmed effective specific treatment for NiV infection in humans to date. The guiding principles are:

- Early implementation of infection control precautions will minimize nosocomical/ household spread of disease.
- Active surveillance, contact tracing and early identification and follow up of persons at risk. Surveillance case definition is placed at **Annexure-II.**
- Provision for dedicated isolation facilities for patients must be created so that laboratory confirmed Nipahcases as well as suspect cases are either kept in individual isolation rooms or cohorted (separate ward for keeping confirmed and suspect cases) in a well ventilated isolation ward with beds kept at-least one metre apart.
- Community contacts and hospital contacts who have gone back to the community are kept in home quarantine. Hospital staff may be kept in home quarantine or in separate individual isolation room facility in a hospital.
- Suspect and probable cases should be hospitalized in isolation facility as described above.
- There should be dedicated doctors, nurses and paramedics well trained in hospital infection control practices and following the standard, contact and droplet precautions to attend to the suspect or confirmed cases.Reinforce standard infection control precautions for all those entering the room must use hand washing practices, high efficiency masks, gowns, goggles, gloves, cap and shoe cover.
- Imaging and laboratory investigations are to be limited till such time laboratory reports are available. This would reduce the risk of transmission of disease among Health Care Workers.
- The isolation facility should have portable X Ray machine, ventilators, large oxygen cylinders, pulse oxymeter and other supportive equipments.
- Adequate quantities of PPE, disinfectants and medications are to be ensured.
- **No accompanying relative or friends of the patient is to be allowed in isolation facility**. Restrict number of visitors and those allowed to visit should be providedwith full protection through PPE.

- Dispose bio medical waste properly by placing it in sealed impermeable bags labelled as Bio- Hazard after decontamination with 5% Sodium Hypochlorite.
- The commonly touched surfaces in the isolation ward should be cleaned with freshly prepared disinfectant (5% Sodium Hypochlorite) every 4 hours.
- Hand sanitizers should be provided at every bed post and exit part of the isolation rooms.
- Any hospital staff getting contaminated should discard the PPE and take a bath immediately with soap and hot water.

4.5.2. General management

- Symptomatic and supportive treatment should be started immediately in all clinically suspected cases. Maintain airway, breathing and circulation (ABC).
- Ensure patient isolation (preferably in a separate ward/room).
- Institute barrier nursing, e.g., personal protection using masks, gloves, gowns, shoe covers and hand-washing with soap and water before and after handling/visiting patients.

4.5.3. Symptomatic and supportive treatment:

a. Patient is advised to drink plenty of fluids.
b. Fluid maintenance and electrolyte balance.
   Fluid restriction, after initial resuscitation, is advisable in order to avoid fluid overload/ complication
c. Nasogastric tube feeding/ parenteral nutrition may be instituted, if necessary.
d. Paracetamol is suggested for fever, myalgia and headache.Salicylate / aspirin is strictly contra-indicated in any Nipah patient due to its potential complications.
e. The cases would be constantly monitored for clinical / radiological evidence of lower respiratory tract infection and for hypoxia (respiratory rate, oxygen saturation, level of consciousness).
f. Patients with signs of tachypnea, dyspnea, respiratory distress and oxygen

saturation less than 90 per cent should be supplemented with oxygen therapy. Types of oxygen devices to be used would depend on the severity of hypoxemia. It can be started from oxygen cannula, simple mask, partial re-breathing mask (mask with reservoir bag) and non re-breathing mask. Disposable cannula only should be used for Oxygen inhalation. In children, oxygen hood or head boxes can be used.

g. Oropharyngeal or endotracheal suction when used should mandatorily be done using a closed suction circuit to avoid dispersal of aerosol in the environment.

h. Patients with severe pneumonia and acute respiratory failure (SpO2 < 90% and PaO2 <60 mmHg with oxygen therapy) must be supported with mechanical ventilation. Invasive mechanical ventilation is preferred choice. Non invasive ventilation is an option when mechanical ventilation is not available. Protocol for management of respiratory failure is given at **Annexure-III.**

i. Anticonvulsants e.g., intravenous diazepam,phenobarbitone, phenytoin or levetiracetam may be used in the standard recommended doses.Mannitol could be used in case of raised Intracranial tension.

j. Suspected cases does not require antibiotic therapy. Antibacterial agents should be administered, if required, as per locally accepted clinical practice guidelines. If required, patients on mechanical ventilation antibiotics should be used judiciously to prevent hospital associated infections.

k. Patients requiring Vasopressors for shock may be started on noradrenalin infusion with or without dobutamine in cases with significant cardiac dysfunction.

l. Use of steroids have not been shown to be effective in managing the neurological/ respiratory involvement.

4.5.4. Drug therapy:

Ribavirin:

As currently there are no strong evidence of proven therapy, it is advisable to administer Ribavirin to all confirmed cases of Nipah virus infection as per the available limited in vitro and in vivo evidences, **subject to approval of Drug Controller General of India [DCG(I)].**

Ribavirin is not a proven treatment for Nipah, and has only single open label trial evidence from Malaysia. But the benefit was significant with 36% reduction in mortality. Therefore, in absence of other treatments, and considering its safety profile, quite well in short term as well as longer experiences with Hepatitis C patients it has been recommended for use in confirmed Nipah infections.The suggested dosesare based on the WHO Guidelines for other hemorrhagic fevers, such as Lassa, Crimean Congo etc.

Dose for Ribavirin

For Adults

- 2000 mg loading (10 tabs of 200 mg)
- Day 1-4 - 1000 mg 6hrly (5 tabs of 200 mg each 4 times daily for 4 days = 80 tablets)
- Day 5-10- 500 mg 6hrly (200 mg each tablet 3 tab - 3 tab - 2 tab - 2 tab at 6hrs gap daily for 6 more days = 60 tablets)

For Children

- Load 30mg/kg,Thereafter,
- for Day 1- 4 to give15 mg/kg 6hrly
- Day 5- Day 10 to give 7.5 mg/kg 6 hrly.

On an average each patient (adult) would require 150 capsules for a 10 days course.

Parentral dose of Ribavirin.

IV Ribavirin

- loading dose of 30 mg/ kg
- then 15 mg / kg every six hourly for 4 days
- Then 7.5 mg / kg every eight hourly for 6 days.

Ribavirin should be diluted in 150 ml of 0.9% Normal Saline and infused slowly.

Adverse reactions of Ribavirin:

Serious Reactions can include haemolytic anaemia, neutropenia, thrombocytopenia, aplastic anaemia, teratogenicity, embryocide, severe depression, suicidal ideation, autoimmune disorders, pulmonary toxicity, pancreatitis, diabetes, hypothyroidism, hyperthyroidism, myocardial infarction, arrhythmias, colitis, retinal haemorrhage, retinal thrombosis, or rarely, hypersensitivity reactions.

Common Reactions can include fatigue, headache, fever, rigors, myalgias, arthalgias, anxiety, irritability, insomnia, alopecia, neutropenia, nausea, vomiting, anorexia, depression, pruitis, dizziness, dyspnoea, anaemia, diarrhea, impaired concentration, cough, rash, or thrombocytopenia.But most adverse drug reactions are in long term therapy as seen in Hepatitis C, not common as in short term therapy.

4.5.5. Newer experimental drugs:

(i) Favipravir has recently been shown to be effective against Nipah viral infections in animal model.

(ii) Immunomodulating drugs have not been found to be beneficial in treatment of ARDS or sepsis associated multi organ failure. High dose corticosteroids in particular have no evidence of benefit and there is potential for harm.

4.5.6. Post Exposure Prophylaxis:

There is no evidence to support the role of ribavirin as post-exposure prophylactic treatment for Nipah fever.

Human monoclonal antibody:

Human Monoclonal antibodies targeting the viral glycoproteins(**anti-G MAb or**

anti-F Mab) against Hendra and Nipah have been shown since 2009 to be highly effective for post-exposure protection on experimental animal. Its use in emergency setting is subject to approval of DCG(I).

4.5.7. Vaccine:

There is currently no approved vaccine that protects against Nipah virus.

4.6. Differential diagnoses

- Dengue
- Japanese encephalitis (JE)
- cerebral malaria
- Scrap typhus
- bacterial meningitis
- herpes simplex encephalitis
- other viral encephalitis

5. Discharge Policy

Nipah confirmed patients should be discharged only after full recovery and the RT-PCR test is negative on the throat swab/ blood sample. However, on discharge, patient is advised to remain in isolation at home till 21 days after the date of positive test. This shall be monitored by the community surveillance team.

Suspected cases kept under isolation must not be discharged before confirmation of negative result.

References;

- The Practical Handbook on Surveillance, Prevention and Control of Nipah Virus Infection ,2011, WHO SEARO.
- Chong HT, Kamarulzaman A, Tan CT, Goh KJ, Thayaparan T, Kunja-pan SR, et al. Treatment of acute Nipah encephalitis with ribavirin. Ann Neurol. 2001,49:810– 13.
- V. Guillaume, H. Contamin,P. Loth, I. Grosjean,M. C. Georges Courbot, V. Deubel, R. Buckland, and T. F. Wild Antibody Prophylaxis and Therapy against Nipah Virus Infection in Hamsters JOURNAL OF VIROLOGY, Feb. 2006, p. 1972–1978 Vol. 80, No. 4 0022-538X/06/$08.00 0 doi:10.1128/JVI.80.4.1972–1978.2006□
- Brian E. Dawes , BirteKalveram, Tetsuro Ikegami , Terry Juelich, Jennifer K. Smith, Lihong Zhang, Arnold Park Benhur Lee, Takashi Komeno, YousukeFuruta& Alexander N. Freiberg. Favipiravir (T-705) protects against Nipah virus infection in the hamster model www.Nature.com (2018) 8:7604 | DOI:10.1038/s41598-018-25780-3
- Bossart KN, Zhu Z, Middleton D, Klippel J, Crameri G, et al. (2009) A Neutralizing Human Monoclonal Antibody Protects against Lethal Disease in a New Ferret Model of Acute Nipah Virus Infection. PLoSPathog 5(10): e1000642. doi:10.1371/journal.ppat.1000642
- National Guideline for Management, Prevention and Control of□Nipah Virus Infection including Encephalitis Directorate General of Health Services Ministry of Health & Family Welfare Government of the People's Republic of Bangladesh Technical support: World Health Organization, Bangladesh Country Office.

Annexure-I

Sample Collection, packaging and Transport Guidelines:

Nipah virus being a BSL-4 agent, universal, standard droplet and bio-containment precautions should be followed during contact with excretions, secretions and body fluids of suspected patient. Adequate biosafety precautions should be adopted during collection/transport/ storage/ processing of suspected sample.

Sample collection: The samples should be collected as early as possible (preferably within 4 days) with all biosafety precautions and accompanied with detailed history of patients on the performa which can be obtained from the testing laboratory (Presently National Institute of Virology Pune in public sector is the testing laboratory which is diagnosing Nipah virus infection based on molecular detection of viral RNA and antibody detection by ELISA).

During sample collection wear complete disposable Personal Protective Equipments (N 95 mask, double surgical gloves, gowns, goggles etc). Wash hands with soap and water atleast for 30 seconds and then clean hand using 1-2 ml alcohol based hand sanitizer before and after collection of samples

The samples may be as follows

- Throat swab in viral transport medium
- Urine 10 ml in universal sterile container
- Blood in plain vial (atleast 5ml)
- CSF (atleast 1 ml) in sterile container

Transportation and Storage of samples: Samples should be safely packed in triple container packing and should be transported under cold chain (2-6°C) to the testing laboratory with prior intimation. Before dispatching the sample disinfect the outer surface of container using 1:100 dilution of bleach or 5% Lysol solution.

Sample containing vials should be kept in good quality plastic bags tide with rubber bands so that inside material if leaks should not come out of bag. The plastic bag should be kept in another container which should be sealed with adhesive tape. This carrier should be placed in another plastic bag sealed with rubber bands and placed in thermocol/vaccine carrier containing ice. The case

sheets with complete information should be placed in plastic bag and should be pasted outside the container.

Samples should be transported at 2-6°C if they arrive at the laboratory with 48 hours; if shipping time is expected more than 48 hours, the samples should be sent using dry ice. Samples should not be held at -20°C for long periods. The sample must be stored at – 70°C if storage is required for longer period.

Annexure-II

Surveillance Case Definition

Suspect Nipah Case

Person from a community affected by a Nipah outbreak who has:

- Fever with new onset of altered mental status or seizure and/or
- Fever with headache and/or
- Fever with Cough or shortness of breath

Probable Nipah Case

Suspect case-patient/s who resided in the same village where confirmed case-patient/s were living during the outbreak period and who died before complete diagnostic specimens could be collected.
OR
Suspect case-patients who came in direct contact with confirmed case-patients in a hospital setting during the outbreak period and who died before complete diagnostic specimens could be collected.

Confirmed Nipah Case

Suspected case who has laboratory confirmation of Nipah virus infection either by:

- Nipah virus RNA identified by PCR from respiratory secretions, urine, or cerebrospinal fluid.
- Isolation of Nipah virus from respiratory secretions, urine or cerebrospinal fluid.

Definition of a Contact:

A Close contact is defined as a patient or a person who came in contact with a Nipah case (confirmed or probable cases) in at least one of the following ways.

- has slept in the same household as a case
- has had direct physical contact with the case (alive or dead) during the illness

- has had direct physical contact with the (deceased) case at a funeral or during burial preparation rituals
- has touched the blood or body fluids (saliva, urine, sputum etc.) of a case during their illness
- has touched the clothes or linens of a case

Annexure-III

Protocol for the ventilator management of patient with Acute Lung Injury (ALI) /ARDS

Indications for Mechanical Ventilation:

Severe Respiratory Failure:Failure to achieve oxygen saturation of > or equal to 90% (or pO2 of > or equal to 60 mm Hg) on an FIO2 < 0.6.

Ventilator Settings:

Pressure pre-set (controlled)Low tidal volume ventilator support.
Tidal volume — 6 ml/kg ideal body weight (Respiratory rate to a maximum of 30-35 per minute).
Open lung strategy of ventilation with PEEP titration to keep the lung recruited to achieve an FIO2 of < 0.5 and a saturation of > 90% or a PaO2 of > 60 mmHg.
Additional use of recruitment manoeuvre is mandatory to ensure prevention of ventilator induced lung injury due to repeated opening and closing shearing injury.
Plateau (Pause) pressure not to exceed of > 30-35 mmHg.
Alternative modes of ventilation APRV (Airway Pressure Release Ventilation), IRV (Inverse Ratio Ventilation) in patients with persistent Hypoxemia (SpO2 of < 88-90% with high PEEP & FIO2 > 0.8).
Rescue therapy — Prone position ventilation, permissive hypercapnia or high frequency ventilation can be considered if above oxygen goals are not met.

If Non Invasive Ventilation for respiratory support is to be considered, it is mandatory to use non-rebreathing mask with use of inspiratory and expiratory tubes through critical care ventilators to reduce spread of infectious aerosols.Use of HEPA filters on expiratory ports of the ventilator circuit / high flow oxygen masks is recommended.